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09/684,794	10/10/2000	Rong Jian Yang		1968

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Raymond Yat Chin Chao
1050 Oak Dale Lane
Arcadia, CA 91006

EXAMINER
HUYNH, PHUONG N

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/684,794	Applicant(s) YANG ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication app ars on th cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-38* is/are pending in the application.

4a) Of the above claim(s) *34-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/26/02 has been entered.

2. Claims 28-38 are pending.

3. Claims 34-38 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected invention.

4. Claims 28-33, drawn to a preparation method of immunoglobulin Y (IgY) against dental caries bacteria are being acted upon in this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 28-31 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The phrase "for 13 months" in claim 28, line (b) represents a departure from the specification and the claims as originally filed. The specification and the claims as originally filed do not provide a clear support for " for 13 months".

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "step (c)" in claim 31 has no antecedent base in base claim 29 because "step (c)" is recited in claim 29. Base claim 29 recites the step (b) comprises the steps of (b1) through (b3).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 28-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang *et al* (J Agric Food Chem 47: 61-66, Jan 1999; PTO 892) in view of US Pat No. 4,4324,782 (April 1982, PTO 892), US Pat No. 5,367,054 (of record, Nov 1994; PTO 892) and Akita *et al* (of record, J. of Food Science: 57(3): 629-634; PTO 892).

Chang *et al* teach a preparation method of immunoglobulin Y (IgY) against dental caries bacteria including the steps of: preparing streptococcus mutants antigen as antigen bacteria by separately culturing streptococcus mutans type c and type d in a culture medium such as brain heart infusion broth for the desired concentration of the bacteria such as culturing for 18 hours and collecting the bacteria by centrifugation and washing the bacteria with sterile saline which is a phosphate buffered saline, pH 7 (See Materials and Methods, in particular). The recitation of

culturing 2-3 days is within the purview of one skill in the art at the time the invention was made to varying the duration of culture to obtain sufficient number of bacteria. Chang *et al* teach the immunodominant sugars in the cell walls of S mutans serotype a, c, e, and f are glucose-glucose while those in the cell walls of S mutans serotype b, d and g are glalactose (See page 63, column 1, fourth paragraph, in particular). Chang *et al* teach human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d and that the antibody against c and d must be applied simultaneously to effectively prevent the human dental caries (See page 63, column 1, second to the last paragraph, in particular). Chang *et al* teach adding adjuvant such as Freund's incomplete adjuvant to equal volume of S mutans and mixed homogenously prior to immunizing hens by hypodermic needle injection of S mutans 1 x 10^9 at CFU/ml each time at once a week for 4 weeks intervals to obtain eggs with active antibody (See page 61 Immunization of Hens, in particular). The reference active antibody against S mutans begins to climb in the third week and last about 13 weeks and then decreased gradually to the 23rd week (See Fig 1, page 63, Effect of Immunization Route on Antibody Activity, in particular). Chang *et al* teach the reference IgY are purified by high methoxy pectin method follows by gel filtration using column such as Sephacryl S-300 and eluting the protein peak with phosphate buffer (PBS) containing 0.85% NaCl in 0.01M phosphate. Fractions of each peak are pooled and the antibody activity of the eluates of the reference protein peaks is estimated with ELISA (See page 62, column 2, Gel filtration, Enzyme-linked Immunosorbent Assay (ELISA), Fig 3, in particular). Chang *et al* teach IgY can be lyophilized and store until ready to be use (See column 62, column 1, first full paragraph, in particular). The recitation of collecting and sterilizing said eggs from 20th day after said first hypodermic injection in claim 29(b2) and claim 32(g) are included in this rejection because Chang *et al* teach active antibody against S mutans begins to climb in the third week which is 20 days after immunization and last about 13 weeks and then decreased gradually to the 23rd week (See Fig 1, page 63, Effect of Immunization Route on Antibody Activity, in particular).

The claimed invention in claims 28(a1) and 32(a) differs from the reference only culturing S mutans type c and type d in a culture medium for 2 to 3 days.

The claimed invention in claim 28(a2) and 32(b) differs from the reference only collecting bacteria by centrifugation.

The claimed invention in claim 28(a3) and 32(c) differs from the reference only washing said bacteria 4 to 6 times with 0.05-0.2M of phosphate buffer saline, pH 6-7 and heating at 50-60°C for 25 to 35 minutes.

The claimed invention in claims 28(a4) and 32(d) differs from the reference only that preparation of IgY against dental carries bacteria wherein the dental carries bacteria streptococcus mutans type c and type d is mixed in a ratio of 2:1.

The claimed invention in claims 28(c), differs from the reference only that the preparation of IgY against dental carries bacteria wherein the crude IgY from eggs is extracted by water dilution method instead of high methoxy pectin method.

The claimed invention in claims 28(d) and 32(n) differs from the reference only that the preparation of IgY against dental carries bacteria by applying the crude IgY on "DEAE-Sephadex A50" column and eluting with phosphate buffer containing 0.07 M of NaCl to obtain eluates of the protein peak instead of Sephacryl S-300 column.

The claimed invention in claims 28(e), and 32(o) differs from the reference only that the preparation of IgY against dental carries bacteria by applying said eluates of protein peak on Sephadex G200 column and eluting with phosphate buffer containing 0.1M of NaCl to obtain new elulates of protein peak.

The claimed invention as recited in claims 28 (h), 31(c5) and 33 (r) differs from the reference only that the preparation of IgY against dental carries bacteria by eliminating bacteria by 0.22μm membrane filtration.

The claimed invention as recited in claims 30(c1), 31(c1) and 32(i) differs from the references only that the preparation step (c) comprises the step of evenly stirring said egg yolks and diluting with 4-6 fold of distilled water to obtain a diluted yolk solution.

The '782 patent teaches antibody against Streptococcus mutans generated from bovine milk can inhibit dental caries (See entire document). The '782 patent teaches cultivating S. mutans such as strains AHT, BHT, 10499 and 6715 separately in culture for 48 hours (2 days) at 37 °C, collecting the bacteria by centrifugation, wash bacteria 5 times with distilled water or physiological saline solution, and heat killed bacteria by heating at 56 °C for two hours, mixing the different strains at 1:1 ratio by suspending the heat killed bacteria in physiological saline solution for immunization (See column 3, lines 16-66, in particular).

The '054 patent teaches a method of preparing egg immunoglobulin Y (IgY) against bacteria *Streptococcus mutans* (See column 8, line 26, in particular) wherein the method steps comprises immunizing hens with a mixture of bacteria such as *Streptococcus mutans* by injection each time at two weeks intervals (See column 8, lines 9-66, in particular), collecting the eggs after hyperimmunization, extracting crude IgY by water dilution such as diluting the separated

egg yolk with 5-30 times deionized water, preferably with 4-6 fold of distilled water (See column 5, lines 38-40, column 2, line 24, in particular), adjusting the diluted yolk solution to pH about 4-6 (See column 5, lines 48-49, in particular), standing the diluted yolk solution at 3-4 °C for at least 2 hr for phase separation (See column 2, line 24, in particular), centrifuging the diluted yolk solution at high speed at about 2500-30,000 rpm to obtain a supernatant (See column 5, line 44, in particular), concentrating the supernatant which is the crude IgY by ultrafiltration (See column 5 line 65-68 bridging column 6, lines 1-2, Example 5, in particular). Following ultrafiltration, the partially pure IgY retentate can be dried by lyophilization (freeze dry) or spray dry (See column 12, example 12, in particular) and/or further purified by sequential ion exchange chromatography such as DEAE column chromatography (See entire document, column 10 line 69 bridging column 11; column 6, line 15; column 6 line 55, Fig 1, in particular), and cation exchange chromatography such as Sephadex column chromatography using the appropriate buffer for the specific column (See column 11, Example 6, example 8, in particular). For ion exchange chromatography, the column matrix that is suitable for large scale IgY purification includes DEAE (diethylaminoethyl)-Sepharose or DEAE-Sephadex wherein the IgY is eluted with DEAE ion exchange buffer (eluant) which is a sodium phosphate buffer containing about 0.01-0.4M NaCl as the final salt concentration (See entire document, column 5 line 49, in particular). Other suitable anion-exchange chromatography materials as well as the selection of using these materials are known to those ordinary skilled in the art (See column 6, line 55, in particular). The '054 patent further teaches egg yolk is a very good source of specific antibodies, the advantages of IgY antibody production is about 100-150 mg/egg and maintenance of higher levels of specific antibodies is relatively easy (See column 1, lines 34-54, in particular). The '054 patent teaches egg yolk (IgY) is a very good source of specific antibodies and that production and maintenance of high levels of specific antibodies is relatively easy (See column 1, lines 34-46, in particular).

Akita *et al* teach a preparation method of extracting egg IgY immunoglobulin by water dilution with six-fold of water, adjusting the pH 5.0 to 5.2, let it stands for at least 2 hr before high speed centrifugation (See entire document, page 629 Materials and Methods) to yield 100mg pure IgY per egg by a combination of ultrafiltration, gel filtration with Sephacryl S-200 using 0.1M phosphate buffer at pH 7.0 and DEAE-Sephacel anion exchange chromatography equilibrate with the appropriate starting buffer (See entire document, Materials and Methods, page 630, in particular) wherein the choice of column depends on the amount of IgY to be purified. Furthermore, Akita *et al* teach that the optimal dilution of egg yolk with six-fold of

water at a pH 5.0 and incubation time of 6 hour at 4 °C gave an IgY recovery of 93-96% (See page 632, right column second paragraph). Akita *et al* teach that the use of gel filtration or anion exchange as the final steps should be most efficient. The advantages of this protocol are that the procedure is simple, rapid and produces high yields of active IgY (See page 633, right column last paragraph, in particular).

The '376 patent teaches purification of immunoglobulin such as anti-B2M simply by initial immunosorbent purification using gel filtration on material such as Sephadex (dextran based) follows by a gel filtration step using material such as Sephadex G-200 to separate the immunoglobulin and impurity on the basis of molecular weight (See column 5, line 11-32, lines 61-68, in particular). The '376 patent further teaches the "best results are obtained with material such as those marketed under the trade names Sephadex G-200" using phosphate buffered saline (See column 5, lines 65-68, column 10, line 39-40, in particular).

The '094 patent teaches sterilizing immunoglobulin by filtration through a 0.22 μm membrane for intravenous injection (See column 10, lines 60-62, Fig 1, claims of '094, in particular). The '094 patent teaches that the advantages of filtration through a 0.22 μm membrane are (1) simplicity, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields (See column 3, lines 1-14, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine S. mutans c and S. mutans d as taught by Chang *et al* or the '782 patent as immunogen for preparing IgY against dental carries as taught by Chang et al, the '782 patent and the '054 patent by extracting the crude IgY from the eggs using the water dilution method as taught by the '054 patent or Akita *et al* and follows by gel filtration chromatograph such as DEAE-Sephadex chromatography as taught by the '054 patent and the "DEAE-Sephadex A50" column chromatography as taught by the '376 patent and eliminating the residual bacteria in the preparation by 0.22μm membrane filtration as taught by the '094 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Chang *et al* teach IgY antibody against both S mutans c and d must be applied simultaneously to effectively prevent the human dental caries (See page 65, Conclusion, page 63, column 1, second to the last paragraph, in particular) since the immunodominant sugars in the cell walls of S mutans a, c, e, and f are glucose-glucose while those in the cell walls of S mutans B, d and g are

glalactose (See page 63, column 1, fourth paragraph, in particular); human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d (See page 63, column 1, second to the last paragraph, in particular). The '054 patent teaches egg yolk (IgY) is a very good source of specific antibodies and that production and maintenance of high levels of specific antibodies is relatively easy (See column 1, lines 34-46, in particular). Akita *et al* teach that the use of gel filtration or anion exchange as the final steps of IgY preparation should be most efficient. The advantages of gel filtration are simple, rapid and produces high yields of active IgY (See page 633, right column last paragraph, in particular). The '376 patent teaches purification of any immunoglobulin by initial immunosorbent purification using gel filtration on material such as Sephadex (dextran based) follows by a gel filtration step using material such as Sephadex G-200 to separate the immunoglobulin and impurity on the basis of molecular weight (See column 5, line 11-32, lines 61-68, in particular). The '376 patent further teaches the "best results are obtained with material such as those marketed under the trade names Sephadex G-200" using phosphate buffered saline (See column 5, lines 65-68, column 10, line 39-40, in particular). The '094 patent teaches that the advantages of filtration through a 0.22 μm membrane are (1) simplicity, (2) speed, (3) the method can be easily scale up and (4) the products are free from virus and can be isolated in higher yields (See column 3, lines 1-14, in particular). Claims 28(a4) and 32(d) are included in this rejection because it is within the purview of one ordinary skill in the art at the time the invention was made to include S mutans d as immunogen since Chang e*t al* teach the immunodominant sugars in the cell walls of S mutans a, c, e, and f are glucose-glucose while those in the cell walls of S mutans B, d and g are glalactose and antibody to both S. mutans c and d should be applied to both simultaneously in order to be effectively prevent human dental caries (See page 63, column 1, fourth paragraph, and page 65, column 2, Conclusion, in particular). The recitation of mixing mutans type c and type d in a ratio of 2:1 is an obvious variation in the teachings of Chang et al who teaches human dental caries is mainly (over 70%) caused by S. mutans c followed by S. mutans d which suggests that the antibody against c and d must be applied simultaneously to effectively prevent the human dental caries (See page 63, column 1, second to the last paragraph, in particular). Claims 29(b3) and 32(h) are included in this rejection because taking out the yolk by sieve is well within the purview of one skill in the art at the time the invention was made. Claims 30(c1), and 31(c1) are included in this rejection because the '054 patent and Akita et al teach diluting the yolks with 5-31 fold water, which includes the claimed diluting with 4-6 fold-distilled water. Claims 30(c2) and 31(c2) are included

in this rejection because the reference pH about 4-6 includes the claim pH 4.5-6.5. Claims 30(c3) and 31(c3) are included in this rejection because standing yolk solution for 20-30 hours for phase separation is within the purview of one ordinary skill in the art at the time the invention was made to practice the claimed invention because the '054 patent teaches standing the diluted yolk solution at 3-4 °C for a minimum of at least 2 hr or longer for phase separation (See column 2, line 24, in particular). Claims 30(c4) and 30(c4) are included in this rejection because centrifugation of any solution to obtain a supernatant is within the purview of purview of one ordinary skill in the art at the time the invention was made to practice the claimed invention as taught by Chang *et al.*

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
December 16, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600